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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/004,494	CHANG, YUNG-FU	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *3,4,12-25,32-46 and 51-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 5-11, 26-31, 47-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11/02/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application filed November 2, 2001is a continuation in part of 09/358,322, filed July 21, 1999, now abandoned.

The preliminary amendment filed December 28, 2001, has been received and entered. The specification has been amended. Applicants amendment filed November 3, 2004 has been received and entered. Claims 24 and 41 have been amended. Claims 1-65 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1, 2, 6-11, 26-31 and 47-50, in the reply filed on November 3, 2004, is acknowledged. The traversal is on the ground(s) that the inventions are not independent nor is there a serious burden to search each of the restricted inventions. Citing MPEP 808.02 Applicants argue that a *prima facie* case has not been made to support the restriction requirement, nor has the need of separate searches of inventions been shown, arguing that a search should include the search of other classes and subclasses (middle to bottom of page 21). Applicants summarize and review each of the relationships and argue that Examiner has not met the burden required by any of the relationships requiring the restriction and request that the restriction requirement be withdrawn (pages 22-25). This is not found persuasive because contrary to Applicants arguments, Examiner has met his burden for requiring restriction of the various inventions. Examiner would not argue that the inventions may be related at some level, however this is not the standard for restriction of separate inventions. The search and consideration of a nucleic acid and its use is unique from that required for a protein,

even though they may be related in that the nucleic acid could be used to produce a protein. Or for other restricted inventions, the search of methodology of PCR would not identify methods of ELISA assays. The search and consideration for one claimed invention would not be required for the other, and even in a general search of the state of the art the search would not be co-extensive because the uses of different products and different methods would each require a specific search of that product and/or method. Applicant's arguments that no extra burden would be required to search and examine all the restricted inventions is not found persuasive because separate unique searches would be required as indicated in the restriction requirement, and would not be co-extensive such that a search of one invention would identify the relevant art for other inventions. Examiner has met the burden of demonstrating the restriction is required by demonstrating different class/subclass, different searches required and that each invention represents divergent subject matter recognized in the art. MPEP 808.02 states that 'the Examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation of one of the following: (A) Separate classification, (B) Separate status in the art when classifiable together, or (C) a different field of search'. Examiner has demonstrated each A-C.

Additionally, it should be noted that Examiner has included with the each claimed product the specific method of use, and thus has considered the burden of search and consideration of the product as claimed for use in the methods proposed by the instant specification. Moreover, each of the specific SEQ ID NOs (for example in claim 1) represent a separate search and consideration for what is encompassed by the claim for that specific SEQ ID NO and for use in any method, however all the sequences have been included in one invention.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-65 are pending. Claims 3-5, 12-25, 32-46, 51-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 3, 2004. Claims 1, 2, 5-11, 26-31, 47-50, drawn to DNA and DNA vaccines and methods of making

Specification

The disclosure is objected to because of the following informalities: the third page of claims is incorrectly numbered 34 (see top of page), it should have been numbered 40.

Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 10 and 11 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 6. When two claims in an application are duplicates or else are so close in content that

they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In this case, claim 10 implies a method of delivery and claim 11 indicates a particular host to which it is used, however neither change the scope of the product in claim 6 as they simply set forth an intended use of the claimed product.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-11, 26-31, 47-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. In the instant case, the specification is not enabling for the claimed invention because the art of gene therapy, in particular the delivery of a DNA vaccine which encode undefined immunogenic epitopes, is highly unpredictable as recognized in the prior art and because the specification as filed does not provide sufficient guidance, evidence and exemplification as to how an artisan would have carried out the claimed methods for expression of any of the specific cloned genes from *E. canis*, wherein the encoded protein stimulates the appropriate immune response such that a prophylactic effect is achieved in said subject.

Claims 1, 2, 5-11, 26-31, 47-50 encompass a vaccine and methods of making said vaccine which protects dogs against *E. canis* infection. Claims 1 and 2 are drawn to recombinant DNA derived from a genomic fragment cloned from *E. canis* and the only use of the DNA taught in the specification is for the production of a vaccine. Claim 5 encompasses any type of vaccine (DNA, protein, attenuated virus,...), dependent claims recite immunogenic

epitopes of five open reading frames from a 5300 base pair genomic fragment of *E. canis*. Further dependent claims recite elements known in the art to increase immunogenicity of DNA fragments and various routes of delivery. The genomic fragment was cloned using antisera from animals which were previously infected with *E. canis,* and the open reading frames in the genomic fragment were deduced by computer analysis and comparison of sequence databases. The five possible open frames are recited in claim 1(a)-(e). The specification does not express nor demonstrate that any of these open reading frames encode a protein in *E. canis* which is detectable by the antisera used in the isolation of the genomic fragment. Further, the specification does not demonstrate that any protein or portion of the encoded proteins identified by the assigned open reading frames on the isolated genomic fragment are immunogenic nor can serve as vaccine against *E. canis*, nor that one can deliver the nucleic acid which encodes the protein whereby expression of said nucleic acid can serve as a vaccine.

The specification provides guidance for the construction of recombinant vectors and recites means of delivery of a polynucleotide to a subject which are known in the art, however the specification is silent with respect to guidance or examples for the use of the assigned open reading frames as immunogenic fragments in a vaccine for *E. canis*. Three points of enablement are at issue; first, the specification demonstrates that antisera from dogs can react with a protein which is encoded by the genomic fragment, however it is unclear what protein epitope or open reading frame encodes the protein which reacts with the antisera. More specifically, it is unclear that any of the five proposed reading frames produce a protein which is normally encoded by *E. canis*. Further, it is unclear that production of a protein from one of the five deduced open reading frames encode a protein from *E. canis* which would produce an immune response in a

dog. Second, the proposed open reading frames in the proper context can encode a protein and there are examples in the art that demonstrate that one can produce an immune response when one injects enough of almost any protein. However, the specification does not demonstrate that any of the proposed reading frames encode an immunogenic epitope, and further, it is not clear that the proteins encoded by the proposed open reading frames produces a prophylactic immune response to *E. canis* infection encompassed by the full scope of the claim. Finally, the claimed vaccine is a DNA vaccine, and the specification relies in great part on delivery methods and expression systems taught by others for the ability to infect the host cells and for the production of the proper amount of the foreign protein to induce an immune response, however there is no guidance nor demonstration that these methods and systems can be used for expression of the proposed open reading frames which result in a prophylactic immune response.

First, the specification teaches the isolation of a genomic fragment from *E. canis* by using antisera from dogs infected with the *E. canis*. This methodology of cloning polynucleotide fragments clearly suggests that a protein encoded by the isolated polynucleotide sequence can interact with antibodies in the antisera. However, the specification does not demonstrate which protein epitope is identified by the antisera. Further, the proposed open reading frames are deduced by computer analysis and there is no clear teaching in the specification that the open reading frames are used in *E. canis* for the production of a protein. For example, SEQ ID NO: 3 is defined as a cytochrome oxidase by sequence homology, but SEQ ID NOs: 5, 7 and 9 have no defined homology or function associated with them, and SEQ ID NO: 11 is incomplete. All the polynucleotide sequences define open reading frames which could potentially encode a protein, but there is no clear indication from the specification that they do. It is not necessary to know

the function of a protein in order to produce an immune response to a protein epitope, however the specification does not demonstrate that the proposed open reading frames do in fact encode a protein which would be useful in generating protein epitopes for use in a DNA vaccine.

Secondly, if the proposed open reading frames were in fact used by *E. canis* in the production of proteins, the specification does not teach what proteins or parts of the proteins contain immunogenic epitopes. Since the genomic polynucleotide was identified and isolated through immunological cloning techniques, it is clear that a portion of the genomic sequence encodes a protein epitope recognized by the antisera, however as discussed above, the specification is silent with respect to which epitope is recognized and what polynucleotide sequence encodes this epitope. Again, it is not necessary to know the function of the protein or even the exact immunogenic fragment which is recognized, however the specification points to five potential reading frames and there is no clear connection between these potential open reading frames and a protein epitope which is recognized by the antisera. There is no clear guidance to which polynucleotide sequences actually encode a *E. canis* protein. Further, as indicated in the specification and the art of record, no successful vaccine for *E. canis* has been developed to date (instant specification page 4, first paragraph). Therefore, while it is clear that dogs can generate an immune response to *E. canis* during the clinical phases of infection and onset of CME, there is no clear indication that use of the encoded proteins from the proposed reading frames would serve as a potential vaccine to *E. canis*. The specification does not clearly teach how to use the described polynucleotides to define immunogenic epitopes, nor does it provide the guidance or the exemplification that the sequences can be used as a vaccine against *E. canis*.

Finally, the specification relies on the vector systems and methods of others for the administration and expression of the encoded protein for use in a DNA vaccine. In a recent assessment of the gene therapy art, Verma *et al.* summarize " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." They further add "the problems- such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions- remain formidable challenges" (see the abstract). Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (page 239; first and second paragraphs in column 1). It is well established in the art that one can use a virus to immunize a subject to produce an immune response, it is often necessary, as in the examples of the present application, to re-administer "booster shots" to stimulate the desired immune response. However, it is not clear from the guidance in the specification, the art of record nor the present state of art how one would produce the effects of immunization through the methods recited in the claim. It is clear that dogs can produce an immune response to *E. canis* after infection as evidenced by antisera used in cloning, however, there is no demonstration that other forms of immune response such as CTL response or stimulation of NK cells was or could be stimulated by the recited method. The humoral immune response which produces IgA and IgG can be generated simply by injecting the foreign protein into an animal. A cellular immune response necessary for a prophylactic effect, however, is more complicated and dependent on appropriate expression levels in a antigen-presenting cell. For example, Bohm *et al.* point out that the relevant antigen-presenting cell that primes responses against antigens after DNA immunization is unknown and the "many promoter

sequences display cell type-specific variability in gene expression" (page 30; second column lines 28-32 and 35-37). Further, Bohm *et al.* demonstrate that of seven vector constructs encoding the viral antigen HBsAg tested in mice, only five were capable of generating an immune response, and of those five, only the three which utilized the CMV promoter efficiently generated both an HBsAg specific antibody and CTL response (page 32; figure 1 and page 38; second paragraph of first column). From a more general view, Verma *et al.* teach that the choice of promoter is critical to the maintenance of transgene expression (columns 2 -3). Therefore, it is unclear from the guidance and examples given in the specification which host cells would serve as appropriate cells for use in the induction of other immune responses, such as CTL, in a subject.

As discussed above, there are several art recognized limitations and unpredictability issues regarding the delivery of a polynucleotide as demonstrated in gene therapy protocols, that include: vector to be used for gene expression, production of effective concentration of the candidate protein, delivery of the protein or gene to target cell, sustained expression and production of the candidate protein *in vivo*, and maintaining an effective level of the protein *in vivo*. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). The specification has not described nor provided examples of how the recited method of delivery of a polynucleotide for the production of a protein epitope differs from those presently found in the art, and in great part rely on the methods of gene delivery established by others, Applicants face the same shortcomings faced by others skilled in the art with regards to the specificity of cell targeting and the ability to regulate gene expression. Besides the general expectation that it will require years of further research to develop effective gene delivery

methods (Verma *et al.*), it would require extensive research to understand the fundamental biology of the system for the development of a vaccine to *E. canis* from the proposed gemonic fragment. Applicants have described deduced open reading frames of a cloned genomic fragment of *E. canis* which may encode protein epitopes, but essentially all of the work required to ultimately define and develop these genomic sequences into methods to produce a prophylactic immune response has been left for others.

In addition, claims 9 and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of specific vectors for expression of the DNA and the methods require the use of the vectors. Since the vectors are recited and essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the cell lines are not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make", may be satisfied by a deposit of vectors. It is noted that review of the specification does not provide any specific sequence information for any of the four claimed vectors. If a deposit has been made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific cell lines have been deposited under the Budapest Treaty and that the cell lines will be irrevocably and

without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807); and,

(e) the deposit will be replaced if it should ever become inviable.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 47, 48, 49, 50 are rejected under 35 U.S.C. 102(b) as being anticipate by Lewis *et al.* (1994).

The claims broadly encompass any polynucleotide seqeuce which encodes an amino acid sequence that can elicit an immune response and vectors capable of expressing said protein. The claim can be reasonably interpreted to encompass any sequence that could serve as an antigen to elicit an immune response because no specific epitope/antigen within the entire sequence is disclosed as being important for producing an immune response. Lewis *et al.* describe the cloning of a *Drosophila* mtDNA, and the sequence specifically disclosed shares stretches of homology that would encode some portion of a protein set forth in SEQ ID NO: 3, 5, 7 and 11. Lewis *et al.* teach the use of expression vectors to screen for inserts, therefore the proteins encoded by the sequences inserted in the vectors of the isolated clones serve a sequence capable of producing a protein that could serve and are capable of producing an immune response.

Conclusion

No claim is allowed.

The complete sequence of each of the SEQ ID NOs encompassed by claims 1, 2, 6-11, 26-31, 47-50 appear to be free of the prior art of record because the prior art of record fails to teach or suggest the claimed polynucleotide sequences or a method of creating a vaccine with said sequences. However, the breadth of the claims encompass any portion or immunogenic

fragment of these sequences. Further, the claims are subject to other rejections as they encompass specific sequences that are vaccines.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (571) 272-0532.

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